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ARE RATS RELEVANT?

by Edward J. Calabrese

Over the past several years there has emerged a widespread recognition that numerous environmental pollutants, consumer products, and certain medications may be carcinogenic. Many people refer to this continuing recognition of carcinogenic agents as the carcinogen of the week club. One day we are told that peanut butter contains a carcinogen, that saccharin causes cancer, that ham and bacon contain nitrite which may form the carcinogen nitrosamine in your stomach, that diesel exhaust is very mutagenic, and that the American Petroleum Institute recommends that self-service gasoline stations put up a warning similar to the one that is on saccharin-sweetened diet soft drinks. While this list could go on and on through hundreds of chemical agents, it is important to realize that much of our information indicating that these compounds are harmful to people comes not from studies with humans, but from experiments with mice and rats. The critical question then is how relevant are rodents in predicting how you and I may respond to such agents? Is a rat just a miniature version of a human or is a human just a big rat? Let's take a look at this issue.

The vast majority of cancer studies are in fact carried out on mice and rats. This is the standard procedure used by our National Toxicology Program. Scientists typically figure out the largest

amount of a chemical that mice or rats can consume without getting noticeably ill, and then feed it to them for most of their adult lives, about two years. This high dose is called the maximum tolerable dose or MTD. The scientists also use a second dose which is usually one-half the MTD. 50 male and 50 female animals are tested for each dose of the chemical, as well as a group given no chemical at all, called the control or comparison group. At a predetermined time, near the normal end of their lives, all of the animals still alive are sacrificed and examined by pathologists for various diseases, including cancer. All of the animals that have died before this predetermined time are also examined in the identical manner.

In order to ensure that no bias influences the outcome of the analysis of the study, the pathologists are given coded specimens so that they don't know which treatment group the specific specimen comes from. Consequently, the study is designed to give as fair an assessment of the study as possible.

This describes in general terms how cancer studies are carried out. The issue still remains — are these studies helpful in predicting how humans respond to the chemicals given to the mice and rats?

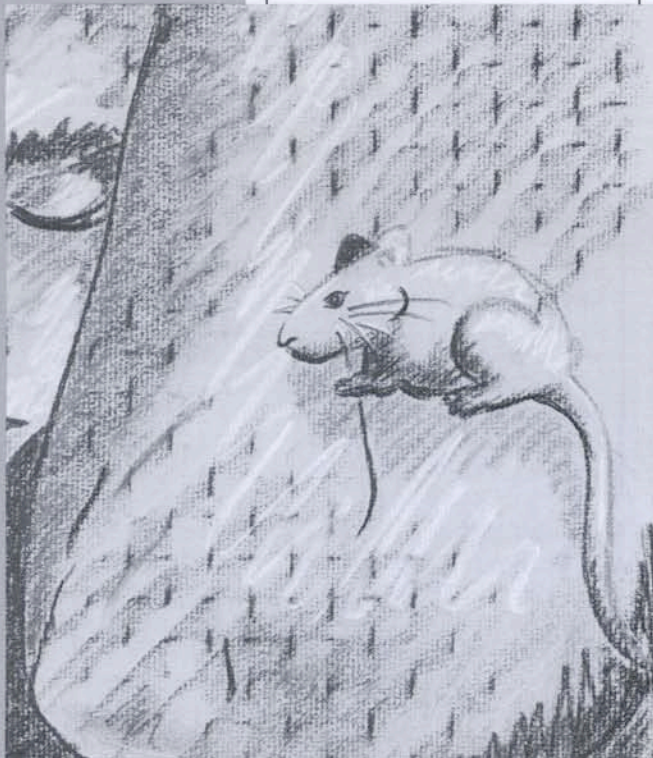
Does it make sense to give the rodents extremely high doses of a suspected carcinogen especially when humans may be exposed to only a tiny fraction of what the animals received? This is a critical issue today. Recall all the commotion over the question of saccharin's potential carcinogenicity. The controversy seemed to stem from the fact that the investigators gave the rat the saccharin equivalent of 800-1000 cans of diet soda each day of their lives. Many in the general public believed that giving such unrealistic exposures to the animal could not be of any relevance to the human condition in which people may drink only a can or two each day. It is interesting to note that the saccharin study was actually one of the most "relevant" studies conducted since many agents are tested at levels which exceed normal human exposure by not just a factor of 1000 times but literally by greater than a million times more!! If the public felt that the saccharin studies did not make any sense in terms of predicting human cancer risk, what must they think about these other studies? Of course, the general public isn't terribly aware of these other studies. Yet it is on the basis of these reports that drinking water standards and concern about hazardous waste areas are evaluated. Why does the

National Toxicology Program use such large doses when cancer studies are conducted and why do many toxicologists both in and out of government believe that using the MTD is the right way to go?

The answer which these people give is based both on science and economics. First the scientific answer. It is assumed that the magnitude of the effect of the carcinogen is directly in proportion to the dose. Using this assumption, no matter how low an exposure may be, some percentage of the population will still be adversely affected. There is therefore no threshold or safe level of exposure. Based on the assumption of directly proportional relationship between dose and effect, it has been argued that every exposure to a carcinogenic agent, no matter how small, will offer some degree of cancer risk. It is further assumed that one can predict what will happen at low doses based on what happens at grossly higher doses such as at the MTD. That, in brief, is the argument that scientists use when they say it is legitimate to extrapolate from high to low doses of carcinogens.

It has been argued that if we use a much larger number of animals, for example 1000 instead of 50 per treatment group, we could use more realistic (as in lower) doses, since the larger number of animals would permit us to detect a lower risk - thus the lower dose. However, since

studies with 50 animals per group already cost over one million dollars and since we never know the actual risk we are dealing with, it just doesn't make any sense to change the current scheme. So, in effect, what the researchers do is to use a small number of rats or mice, give them the highest dose they can handle over a lifetime, and then somehow extrapolate down to a lower, more realistic dose. Does this make sense? If not, are there ways it could be improved?



Julie Polvinen

At the present time, the best argument supporting the current testing system is financial and not scientific. The assumption that one can predict cancer risk from the consumption of one soda per day based upon responses observed at grossly higher levels (for example, 1000 cans per day) is just that, an assumption. It is quite possible that nothing bad may happen at low levels of exposure. While the body may not be able to deal effectively with a massive chemical challenge, it may work just fine if the carcinogen is given in minute

amounts. If this is true, then the whole premise of the current cancer program is undermined. This, in fact, is true for a whole new class of carcinogens which apparently act on the body without attacking its DNA. However, untenable as some of the assumptions used by toxicologists doing animal cancer studies may seem, finding acceptable alternatives to the current problems which are scientifically defensible while not breaking the bank are few and far between.

Given that scientific approaches seem to be at a standstill with regard to improving the current situation, the major driving force for change is, as stated before, financial. Why? We have literally tens of thousands of chemicals which we desperately need to evaluate for their potential carcinogenicity. If each one were to cost over a million dollars, the total cost just for cancer evaluation, not even considering all of the other possible health concerns, would be astronomical. Consequently, there are strong efforts being made to try to shorten or even circumvent the lifetime cancer studies with shorter, less expensive studies which can reliably predict whether an agent may be carcinogenic. However, all known short-term predictive tests for carcinogenicity are inherently limited in their ability to predict the actual risk of cancer. Often just knowing that an agent may cause cancer is not enough information. Our society needs to know what the risk or chance of developing cancer is for each dose level of a chemical. Thus, we should try to find a way to incorporate the enormous benefits of our technological achievements while at the same time not falling victim to them.

Now let's investigate how well rats and mice simulate the human organism and why they are presently used in cancer studies.

Have you taken a walk through a pet store recently and stopped to look at the mice? Do these little furry creatures, with pointed noses, whiskers and four legs remind you of yourself? Believe it or not, your health and life and that of your family depends on the ability of mice and rats to predict how humans respond to toxic and carcinogenic agents. Thousands of substances are allowed to be used in foods and other consumer products on the basis of how they affect mice and rats. If these animals don't develop cancer or any other horrible diseases, the government will usually give its O.K. and before you know it we are eating the foods or wearing the products. What confidence should you have that your health and life are being adequately protected by our current testing scheme?

Let's take a look at why the government uses rodents to predict how we may respond. The rodents are used not because they are excellent models to predict human responses or even because they are the best models. They are used because of practical reasons which include their cost, resistance to infectious diseases, relatively short life span, and ability to develop pollutant-induced diseases. While many scientists feel that monkeys may be better models for humans, they are not used in alternative studies because of their poor availability, high cost, and longer life-span. You need an animal model that can tell you relatively quickly if an agent causes cancer; waiting 10-20 years for the answer is just too long for society to remain in suspense, even if the study has a significantly better chance of being correct. Even the 2-3 years of a rodent's life seems too long given the need to know whether a substance is a carcinogen. These practical considerations are powerful arguments in deciding which animal should be used.

Given the practical reasons for why we should use rodents, what about the biological reasons? That is, can these animals predict how you and I will respond?

This is a most difficult question to resolve. The answer, as I see it, is that the rat can give a fairly decent indication of how an agent may affect people. In other words, like an archer, often times we will hit the target but don't expect us to hit the bull's-eye. Take, for example, the cases of asbestos, vinyl chloride and cigarette smoke. All three are human carcinogens and all three cause cancer in rodents. In contrast, arsenic is also a known human carcinogen. However, arsenic has been tested over a dozen times in mice and rats and has never been found to cause cancer. Getting 3 out of every 4 right on tests in school means you pass the test. However, when we are dealing with potential cancer causing agents, even one wrong out of 1000 is unacceptable given the untold misery the mistake is likely to cause.

That studies using the rat should miss one every now and then is not unexpected. Despite some striking similarities between humans and rodents, there are many differences which can easily spell the difference between developing cancer or not. For example, rodents have different numbers and types of bacteria living in their digestive tracts than people; they tend to excrete a higher proportion of heavier compounds through the bile; they synthesize ascorbic acid in their livers; they don't have gall bladders; they concentrate their urine much more; and they always breathe through their noses, among many other differences. Given so many differences, it is often surprising that they do as decent a job as they do!

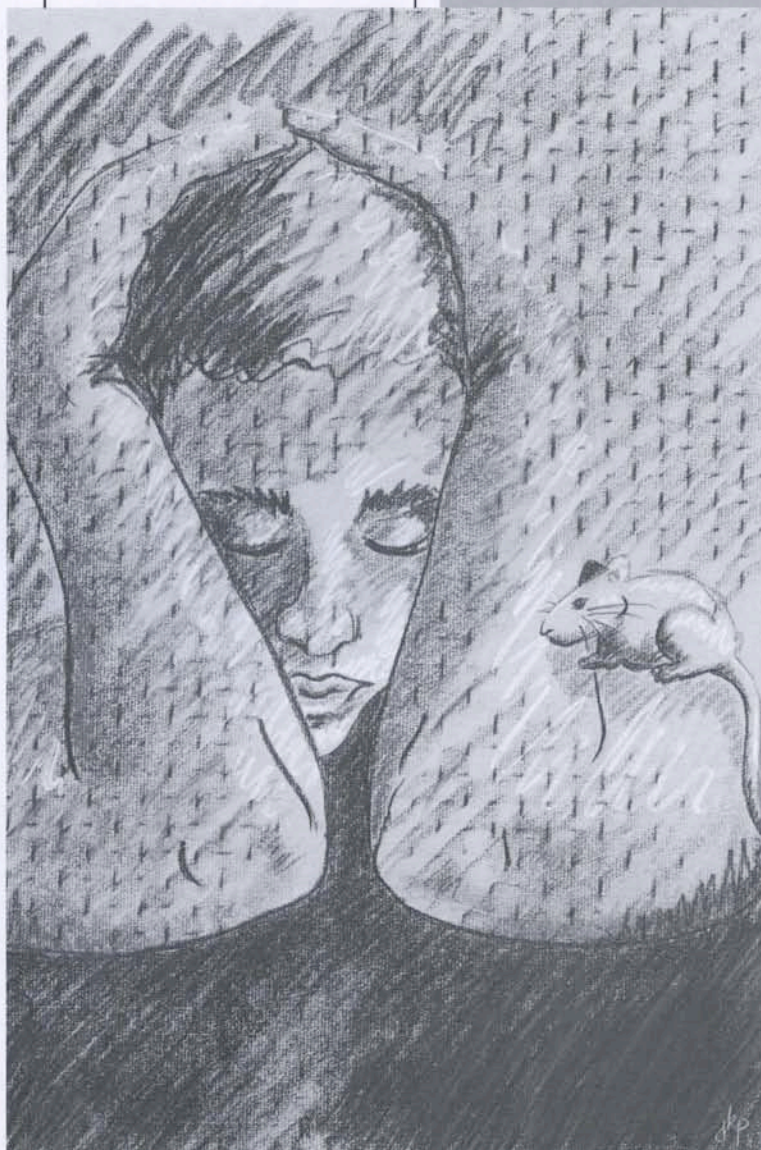
It is because of the inherent limitations of any one species

to predict accurately how humans may respond that the National Toxicology Program uses not one but two species - mice and rats - in their testing scheme. Presumably, they figure that if one species doesn't pick out the adverse health effect, then maybe a second one would. Using two species, in fact, played an important role in the study sponsored by the American Petroleum Institute on the carcinogenicity of unburned gasoline. In that case, only the male rat was sensitive. If only the mouse had been used, then the cancer effect would have been missed. This type of redundancy in the testing system is thought to help ensure that a carcinogen will not slip through.

The interesting thing about the current testing programs is that we really don't know how successful they are. It is very hard to later prove that "compound X" which caused cancer in the rats was, or wasn't carcinogenic in humans. Human population studies are generally somewhat insensitive unless we are dealing with a very rare type of cancer (as in the case of vinyl chloride-induced angiosarcoma) or a very potent carcinogen (as in the case of cigarette-smoking asbestos workers). The current situation reminds one a little of a comment that Senator Howard Baker made about Reaganomics in the early 1980's. He said that the economic course Reagan was charting for the country was a "river boat gamble." At least in the case of President Reagan's program, one can tell after a certain number of years if it was the right way to go. However, in the case of cancer testing programs one may never know.

Finally, it has become

fashionable in scientific circles to discuss the cancer risks of various activities. For example, drinking a quart of water each day with a chloroform level of 100 parts per billion, the level allowed by the EPA, is thought to have a risk of causing four cancers per 10,000 persons over a lifetime. One flight from Boston



to L.A. and back will increase one's risk of cancer by one in a million because of the extra amount of cosmic rays you receive at that high altitude. Eating 20 peanut butter sandwiches will also increase your cancer risk by one in a million because of the carcinogenic contaminant called aflatoxin found in most commercially available brands.

Now we read that as little as a trillionth of a gram of dioxin in a cubic meter of air is predicted to produce about 100 additional cases of cancer for every million people. Just what are these numbers or risks based on?

These numbers are really predictions of what experts think will happen based on previous studies, usually with mice or rats. Only in very limited situations are these predictions based on human studies. As previously discussed, the typical situation involves scientists conducting a study in which the animal receives a very high dose of a chemical over its entire lifetime. If the substance causes cancer in the animal, then predictions like the ones we are talking about are made. The key element here is that we are trying to predict what will happen at very low levels of exposure based on studies in which grossly higher levels were used. If the findings of a study are positive, mathematicians apply certain formulas to the cancer data. These mathematical manipulations allow us to calculate a risk at any level of exposure one desires to know. This process of predicting what will happen at doses beyond those used in a study is called extrapolation. The further the doses are from those used in the study the more risky the endeavor.

But, now for a simple question. How can one tell if a prediction is correct or even close to being correct? The sad fact of the matter is that these cancer risk predictions can never really be proven or disproven. Why? Consider the question: How would you even prove that a risk exists for one cancer in a million people over a 70 year lifetime? To do this you would need over 70 years to conduct the study, the size of a budget that only Fort Knox could hold, and the luck of a dozen Irish sweepstakes winners. The simple fact is that the

risks are calculated without the intention to try the impossible - that is, to validate them!

Another important point to consider in this whole process is that when these risks for humans are calculated based on animal studies, it is assumed that the human and rat (or mouse) respond in an identical way to a carcinogen. Of course, this could not be true. Nevertheless, this is an assumption that is always made. Nobody knows whether the rat may be more or less sensitive, nor how much more or less. All in all,

cancer risks is a new discipline in the field of public health. Although we as a society may need and, in fact, demand accurate answers, we should fully understand the limitations of current approaches. Consequently, in my opinion, the value of current risk predictions is not the calculated risk we are told, because this could be way off the mark. The real value at present lies in the ranking of chemical agents and activities so that regulatory agencies may identify the most important areas where action is needed.

What then is the bottom

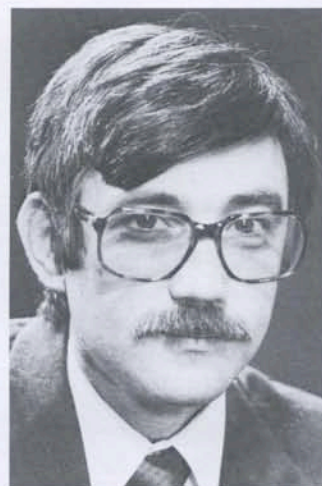
Much more, however, is needed and it can proceed with the continued support of the American public to demand that quality of our scientific database and judgments in this field of toxicological risk assessment be maintained and expanded — because without such improvements the enormous uncertainties we face can undercut the basic right to a safe and healthy environment. ■

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the process whereby toxicologists go about predicting cancer risks is heaped with uncertainties.

Since the process used to predict cancer risk is based on several questionable assumptions and cannot be empirically verified, predicting cancer risk is problematic. However, society needs to begin to get answers to these questions. To be able to differentiate between activities and products on the basis of cancer risk is important in establishing government policy, developing drinking water and air quality standards, and affecting the public's choice of activities. However, the scientific community and the general public must realize that the process of predicting

line here? It is that the toxicological community faces a series of extraordinary challenges as it tries to accurately predict whether a future drug, food additive, or pesticide is not only able to do its intended job but to do it in a manner that does not adversely influence the public's health. Current procedures have many limitations and yet decisions have to be made. We truly hope that our testing procedures are up to the task of protecting the public. But enough exceptions or failures exist to preclude overconfidence. We must recognize that the demands on the toxicologist often exceed the capacity of this science to deliver the answers we need. Yet, progress has been made.



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Dr. Calabrese has researched extensively in the area of host factors affecting susceptibility to pollutants. He is the author of more than 200 papers in refereed journals and ten books and writes reviews for 10 journals.

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